PREVALENCE OF HYPOTHYROIDISM IN RECURRENT PREGNANCY LOSS IN FIRST TRIMESTER

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ABSTRACT

AIM: To determine the frequency of hypothyroidism in women with recurrent pregnancy loss in first trimester in the Indian population. SETTINGS AND DESIGN: The study included 163 non-pregnant women with recurrent pregnancy loss in a gestational age up to ≤12 weeks verified by a pregnancy test or ultrasonography, and a total of 170 age matched women with at least one successful pregnancy and no history of miscarriages were selected as controls. METHODS: Levels of thyroid hormones T3, T4 and TSH were estimated in non-pregnant women with RPL and controls. RESULTS: Hypothyroidism was found in seven (4.12%) women with RPL and one in control group. The differences in the levels of serum T3, T4 and TSH between euthyroid and hypothyroid women were found significant in women with RPL in first trimester. STATISTICAL ANALYSIS: The statistical analyses were performed with the use of student's two-tailed t-test. CONCLUSION: The study demonstrates that hypothyroidism has a statistically significant relationship with recurrent pregnancy loss in the first trimester and suggests that diagnosis of hypothyroidism could help couples with recurrent pregnancy loss to have a successful outcome in subsequent pregnancies.

Key words: Hypothyroidism, recurrent pregnancy loss, risk factor

INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as three or more consecutive spontaneous pregnancy losses before 20 weeks of gestation. Pregnancy loss in the first trimester is the most common complication affecting approximately 15-20% of clinically recognized pregnancies.[1] RPL is a heterogeneous condition.

Hypothyroidism is linked to recurrent pregnancy loss.[2,3] Thyroid hormones are essential for the growth and metabolism of the growing fetus. Early in pregnancy, the mother supplies her fetus with thyroid hormones. If the mother is hypothyroid, she cannot supply her fetus with enough thyroid hormones. Hence hypothyroidism is a risk factor for pregnancy loss. However, the correlation between maternal and fetal thyroid status is poor, and hypothyroid mothers frequently deliver euthyroid infants. Nevertheless, thyroid disorders in early pregnancy may lead to grave consequences, and therefore testing may be

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appropriate.[4] The prevalence of sub-clinical hypothyroidism in women in the childbearing age may be as high as 5%.[5,6]

The role of antithyroid antibodies in pregnancy loss is controversial. Rushworth *et al.*[7] and Esplin *et al.*[8] found no association between antithyroid antibodies and recurrent pregnancy loss whereas Abramson and Green[9] and others[10] found an association between the two. As these studies could not emphasize that thyroid auto antibodies are responsible for fetal loss we evaluated only the thyroid hormones in our study. Since studies in first trimester pregnancy loss are meager in the Indian population, the present study is aimed at determining the thyroid status in women with RPL in first trimester and controls by estimating the serum thyroid hormone concentrations to assess the relationship of hypothyroidism with RPL.

MATERIALS AND METHODS

The study was performed on 163 non-pregnant healthy women with two or more spontaneous consecutive first trimester pregnancy losses between September 2000 and July 2005 at the Institute of Genetics and Hospital for Genetic Diseases, Osmania University, Hyderabad. One hundred and seventy healthy age-matched women without a history of abortion were included in the control group.

The Institutional Ethical Committee at the Osmania University, Hyderabad, India, approved the study**.** All the women were thoroughly examined clinically at the Institute. Particulars pertaining to their age, place, health status, menstrual history, consanguinity, pedigree and previous medical and reproductive data were recorded in prescribed case sheets. All the women selected for this study were non-pregnant and non-diabetic with normal uterine anatomy, normal peripheral blood karyotype and anticardiolipin antibody negative and negative for TORCH infections and their spouses were non-diabetic with normal karyotype, normal sperm count and normal sperm morphology. After obtaining an informed and written consent from the couples in the study and control groups 2 mL of blood from each woman were collected and serum was separated and stored at -20°C in small aliquots for thyroid hormonal investigations.

The quantitative estimation of tri-iodothyronine (T_3) and Thyroxin (T_4) hormone levels in serum samples was carried out by radio immunoassay (RIA) technique. The procedure follows the basic principle of competition between a radioactive and a non-radioactive antigen for a fixed number of antibody binding sites. The normal range of serum T_3 is 70-200 ng/dl and that of T_4 is 5.0-12.5 µg/dl. The quantitative estimation of Thyroid Stimulating Hormone (TSH) was carried out by immunoradiometric assay (IRMA). It is a non-competitive assay in which the analyte to be measured is sandwiched between radiolabelled and unlabelled antibodies. The normal range of serum TSH is 0.3-5.0 µIU/ml.

RESULTS

The mean maternal age of the 163 women with RPL was observed as 25.19 ± 4.01 years. The mean paternal age was 30.46 ± 4.18 years. 50 (30.67%) out of 163 women with RPL had consanguineous marriages, and first cousin

marriages (62%) were frequent whereas in control group 25 (14.71%) out of 170 women had consanguineous marriages and first cousin marriages (84%) were frequent. In the present study 87 (53.37%) women experienced three or more pregnancy losses and 76 (46.63%) women experienced two losses.

Thyroid hormones: In seven (4.29%) women with RPL, hypothyroidism was found to be causative for abortion. Out of seven, in three cases consanguinity was observed. In four cases two pregnancy losses and in three cases three or more losses were observed. In the control group one (0.61%) woman was identified with hypothyroidism. The normal range considered for serum T3 is 70 to 200 ng/dl; for T4 5.0 to 12.5 µg/dl and for TSH 0.3 to 5.0 µIU/ml. The mean ±SD values of serum T_3, T_4 and TSH levels obtained in euthyroid and hypothyroid patients and controls are shown in Table 1.

Statistical analysis

The statistical analyses were performed with the use of student's two-tailed t-test. The differences in the levels of T_3 ('t' = 3.61898, df = 161 and CI = 41.73-71.35) and T_4 ('t' = 20.9772, df = 161 and CI = 2.74-4.94) between euthyroid and hypothyroid in the patient group were found statistically highly significant (P < 0.001) whereas it was significant (P = 0.015) for TSH ('t' = 2.4522, df = 161 and CI = 29.06-30.72). As there was only one hypothyroid case found in the control group, test of significance could not be carried out between euthyroid and hypothyroid women in controls. The differences in the levels of T_3 ('t' = 7.8959, df = 323 and CI = 116.74-124.24), T_4 ('t' = 6.45756, df = 323 and CI = 7.86-8.30), and TSH ('t' = 4.8718, df = 323 and CI = 2.43-2.91) between euthyoid patients and euthyroid controls were found statistically highly significant (P < 0.001). The results indicate that hypothyroidism is associated with recurrent pregnancy loss.

DISCUSSION

Thyroid hormones are essential for the sustenance of the developing fetus. Hence a hypothyroid pregnant woman needs thyroxin treatment more than ever because she must provide T_4 for both herself and her developing fetus. The fetus's thyroid gland is not fully functional until after 12 weeks of pregnancy. If the mother does not have sufficient thyroid hormones, she may be at increased risk of miscarriage. Since the majority of women are not sure that they are pregnant until four to six weeks after the last menstrual period, they don't go in to see doctors and test their thyroid function until the first trimester is more than half over. Hence it is advisable to suggest

Table 1: Mean ± S.D. of Serum T3, T4 and TSH levels in hypothyroid and euthyroid women

With recurrent pregnancy loss and controls

Type of thyroidism	*Mean T3 levels ng/dl*	*Mean T4 levels µg/dl*	*Mean TSH levels µIU/ml*
Study group (n = 163)			
Euthyroid (n = 156)	120.49±19.99	8.08±1.48	2.67±1.12
Hypothyroid (n = 7)	56.54±9.05	3.84±0.62	29.89±29.37
Control group (n = 170)			
Euthyroid (n = 169)	127.62±23.89	8.43±1.37	2.29±1.54
Hypothyroid (n = 1)	47.29	3.87	11.38

to the pregnant women to go in for thyroid testing as soon as possible after knowing they are pregnant.[11] Tina *et al.* found that pregnant women treated for hypothyroidism were not at any increased risk for perinatal morbidity compared with pregnant euthyroid women.[12] Canaris *et al.* and Hollowell *et al.* found the overall prevalence of sub clinical hypothyroidism to be as high as 5% in women of childbearing age.[5,6] There may be no harm in treating patients with sub-clinical hypothyroidism, as long as they are given the correct thyroxin dose. However a joint statement on management of sub-clinical thyroid dysfunction from the American Association of Clinical Endocrinologists, the American Thyroid Association and The Endocrine Society believes that many patients with persistent serum TSH elevations of any degree will benefit from thyroxin therapy and that the physician's judgment, in conjunction with the patient's input, should be paramount in this decision-making process.[13] Sharma *et al.* found no significant differences in pregnancy outcome when hypothyroid pregnant women on thyroxin therapy were compared with euthyroid pregnant women in the Indian population.[14] Vinita *et al.* found hypothyroidism in 1.44% of women with recurrent pregnancy loss in the Indian population.[15] Stray-Pedersen and Stray-Pedersen detected thyroid dysfunction in 2% of women with recurrent pregnancy loss.[16] Tulppala *et al.* detected sub-clinical hypothyroidism in 8.3% of secondary aborters.[17] In the present study, hypothyroidism was found to be causative for abortion in seven (4.29 %) women with RPL in the first trimester in an Indian population.

Consanguinity has been known to increase the chance of the husband and wife carrying an identical gene derived from a common ancestor. Children of such a marriage, therefore, are at greater risk of being homozygous for a harmful gene and consequently suffer autosomal recessive genetic disorders.[18] In India consanguineous marriages are common as people prefer to marry within their clan. Nath *et al.*, 2004 observed a higher rate of fetal losses in Indians in a consanguineous group compared to a non-consanguineous group.[19] Women with personal or family history of thyroid disease or with symptoms suggestive of hypothyroidism should be tested for thyroid hormone levels. In the present study consanguinity was found in 30.67% of cases with RPL and the most frequent type of consanguineous marriage was between first cousins (62%).

Hence this study demonstrates that hypothyroidism has a statistically significant relationship with recurrent pregnancy loss in first trimester and suggests that diagnosis of hypothyroidism could help women with two or more recurrent pregnancy losses in the first trimester to have a successful outcome in subsequent pregnancy.

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REFERENCES

1. Hassold T, Abruzzo M, Adkins K, Griffin D, Merrill M, Millie E, *et al.* Human Aneuploidy: Incidence, origin and etiology. Environ Mol Mutagen 1996;28:167-75.
2. Allan WC, Haddow JE, Palomaki GE, Williams

JR, Mitchell ML, Hermos RJ, *et al.* Maternal thyroid deficiency and pregnancy complications: Implications for population screening. J Med Screen 2000;7:127-30.
3. Moghissi KS. What causes habitual abortion? Contemp Ob Gyn 1982;20:45.
4. Kalro BN. Impaired infertility caused by endocrine dysfunction in women. Endocrinol Metab Clin North Am 2003;32:573-92.
5. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.
6. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, *et al.* Serum TSH, T4 and thyroid antibodies in the United States population (1988-1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-99.
7. Rushworth FH, Beckos M, Rai R, Chicott IT, Baxter N, Regan L. Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid auto antibodies. Hum Reprod 2000;15:163-79.
8. Esplin MS, Branch DW, Silver R, Stagnaro-Green A. Thyroid auto antibodies are not associated with recurrent pregnancy loss. Am J Obstet Gynecol, 1998;179:1583-6.
9. Abramson J, Stagnaro-Green A. Thyroid antibodies and fetal loss: An evolving story. Thyroid 2001;11:57-63.
10. Prummal MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. Eur J Endocrinol 2004;150:751-5.
11. Williams GH, Lily LS, Seely EW. The heart in endocrine and nutritional disorders. In: Heart disease - a text book of cardiovascular medicine: 5th ed. W.B. Saunders Company; Chapter 61, 1997. p. 1885-913.
12. Tina TO, Yvonne CW, Aaron CB. Are women who are treated for hypothyroidism at risk for pregnancy complications? Am J Obstet Gynecol 2006;194:e1-3.
13. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Sub-clinical thyroid dysfunction: A Joint statement on Management from the American Association of clinical endocrinologists, the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab 2005;90:581-5.
14. Sharma PP, Mukhopdyay P, Mukhopadyay A, Muralidharan P, Begum N. Hypothyroidism in pregnancy. J Obstet Gynecol India 2007;57:331-4.
15. Vinita D, Anjoo A, Premlata Y, Agarwal CG. Endocrinological factors and recurrent abortion. J Obstet Gynecol India 2003;53:234-6.
16. Stray-Pedersen B, Stray-Pedersen S. Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol 1984;148:140-6.
17. Tulppala M, Palosuo T, Ramsay T, Miettinen A, Salonen R, Ylikorkala O. A prospective study of 63 couples with a history of recurrent spontaneous abortion: Contributing factors and outcome of subsequent pregnancies. Hum Reprod 1993;8:764-70.
18. McKusick V. Human genetics, 2nd ed. New Delhi: Prentice Hall of India; 1972. p. 145-9.
19. Nath A, Patil C, Naik VA Prevalence of consanguineous marriages in a rural community and its effect on pregnancy outcome. Indian J Community Med 2004;1:41-3.

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